

2' Much of a Problem with Hypoglycaemia

N Sukumar¹, H Venkataraman¹, J Ayuk^{1,2}

¹Department of Endocrinology, University Hospital Birmingham, ²University of Birmingham

Case Overview

- Endocrine referral: 2x hypoglycaemic episodes in non-diabetic patient
- 88 year old man
- Admitted under oncology 4 weeks previously with pulmonary oedema and blocked ureteric stent 11 days after palliative trabectedin
- Nocturnal hypo – CBG 1.2 when found unrousable from sleep, IV glucose given
- Patient denied any symptoms when questioned

Past medical history

- Metastatic malignant fibroma of pelvis
 - CT (10/16): 16cm pelvic mass with small volume lung nodules
 - Histology (12/16): solitary fibrous tumour, STAT6 positive, Ki67 30
 - For palliative chemotherapy only
- Bilateral hydronephrosis, ureteric stents: 01/17
- Bilateral nephrostomies: 03/17 (for blocked stent and worsening AKI)
- Decompensated heart failure, NYHA Class 3
- Drug history → Bisoprolol 2.5mg OD, Fortisip liquid TDS, Hyoscine butylbromide PRN, Midazolam S/C PRN, Oxynorm IV PRN, Paracetamol 1g QDS
- Social history → lives alone, independent ADLs until diagnosis
 - Retired machinist
 - Non smoker, occasional whiskey

Investigations

- Initial investigations:-

Test (units)	Result	Normal range
Urea (mmol/L)	22.5	3.4 – 8.0
Creatinine (umol/L)	352	60 - 126
eGFR (ml/min)	13	
Cortisol (nmol/L)	412	> 350
TSH (mIU/L)	1.85	0.3 – 4.5

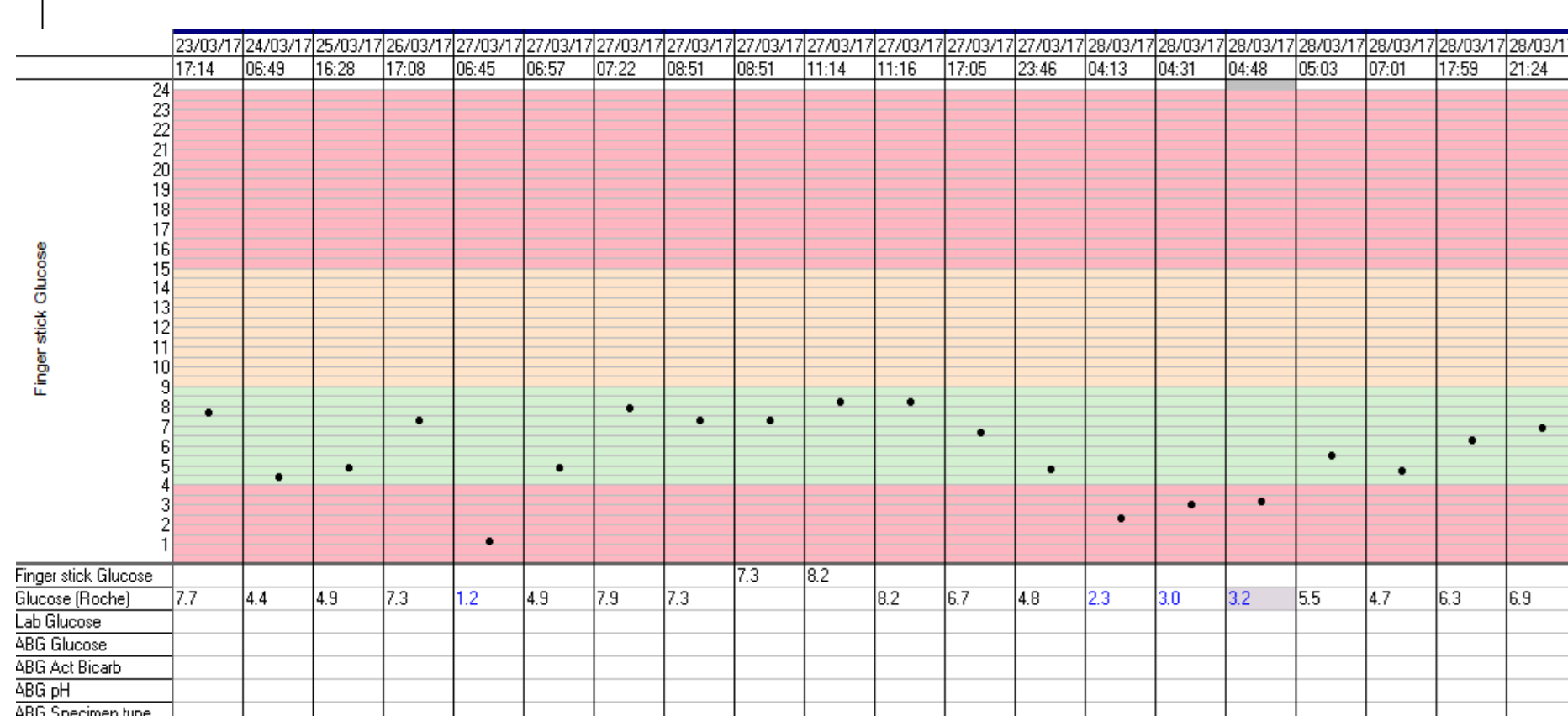
- Additional blood tests requested during next hypo prior to treatment
↓next night
- CBG 2.7 mmol/l – bloods sent off

Test (units)	Result	Normal range
Glucose (mmol/L)	2.2	3.5 – 11
Insulin (pmol/L)	< 10	>20
C-peptide (nmol/L)	380	
IGF-I (nmol/L)	7.1	4.6 – 23.4
IGF-II (nmol/L)	137.2	
IGF-II: IGF-I ratio	19.3	<10

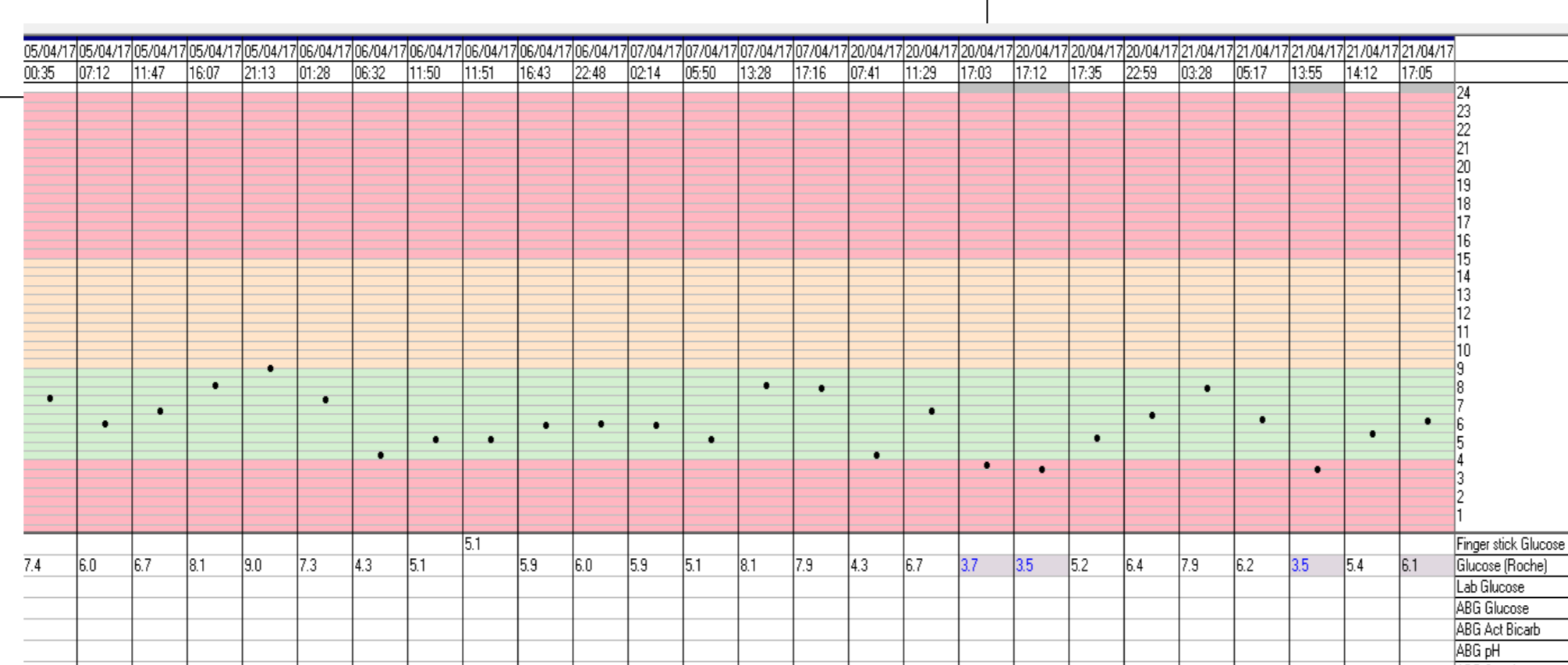
Management

- Started Prednisolone 10mg BD → 5mg BD on discharge

Initial blood glucose chart



Post-steroid blood glucose chart



Discussion

Causes of hypoglycaemia

Insulin mediated	Non-insulin mediated
Drugs ❖ Exogenous insulin ❖ Insulin secretagogues	Drugs ❖ Alcohol ❖ Pentamidine, quinine, indomethacine
Insulinoma	Critical illness ❖ Hepatic / renal / cardiac failure ❖ Sepsis
Functional beta-cell disorders (nesidoblastosis) ❖ Noninsulinoma pancreatic hypoglycaemia ❖ Post gastric bypass 'dumping syndrome'	Hormone deficiency ❖ Cortisol ❖ Glucagon / adrenaline
Insulin autoimmune hypoglycaemia	Non-islet cell tumour
Accidental / surreptitious hypoglycaemia	

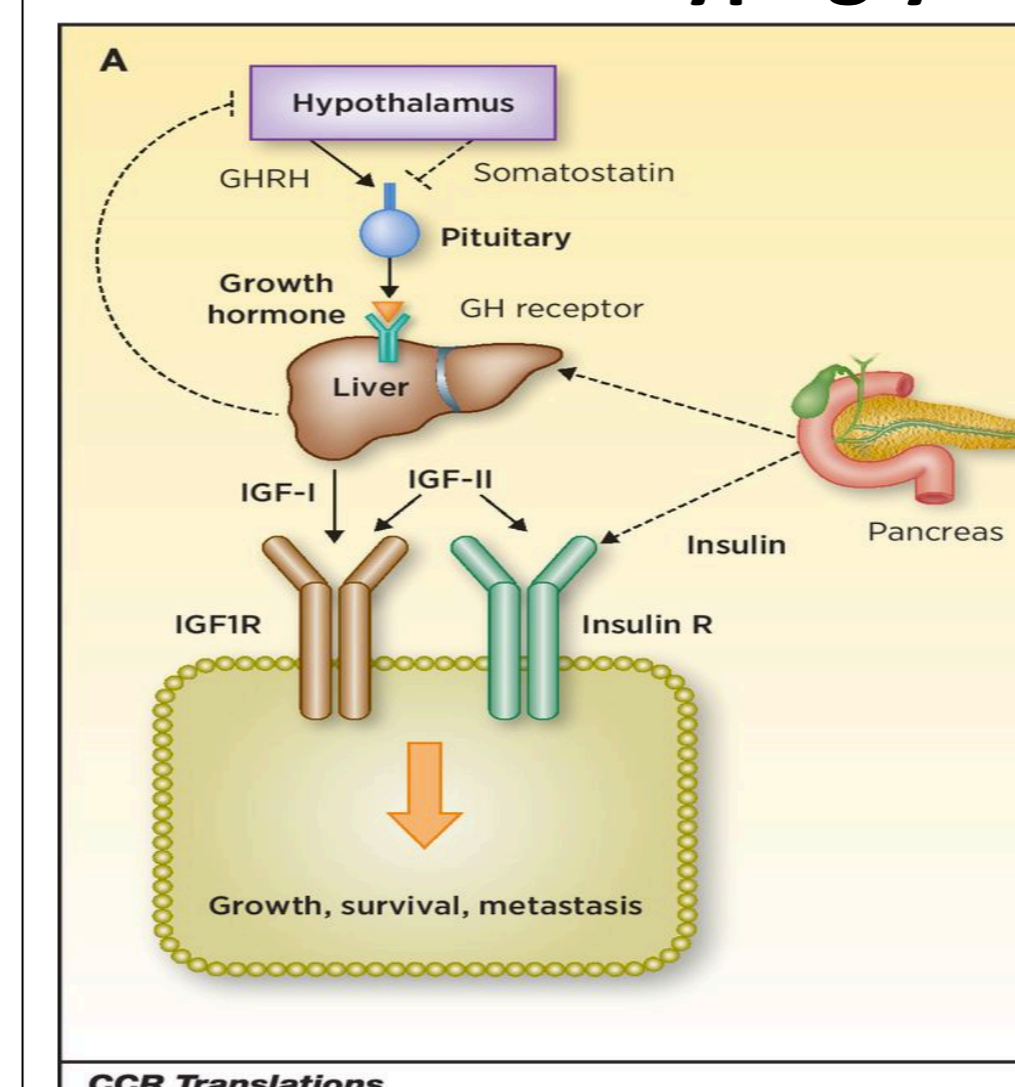
Non-islet cell tumour hypoglycaemia

- Complication of certain malignancies resulting in symptomatic severe hypoglycaemia (usually in fasting state)
- ~130 case reports / small series in English language medical literature in last 30 years¹
- Occur with < 5% of solitary fibrous tumours

Pathophysiology

- Tumours of mesenchymal or epithelial origin¹
 - Solitary fibroma / fibrosarcoma or mesothelioma (22%)
 - Hepatocellular carcinoma (17%)
 - Hemangiopericytoma (7%)
 - Adrenal carcinoma, pheochromocytoma
- 2/3 retroperitoneal, 1/3 thoracic
- 70% of tumours >10 cm in diameter²
- 'Big' IGF-II formed from abnormal processing of pro IGF-II in tumours with aberrant gene transcription / expression

Mechanism of hypoglycaemia

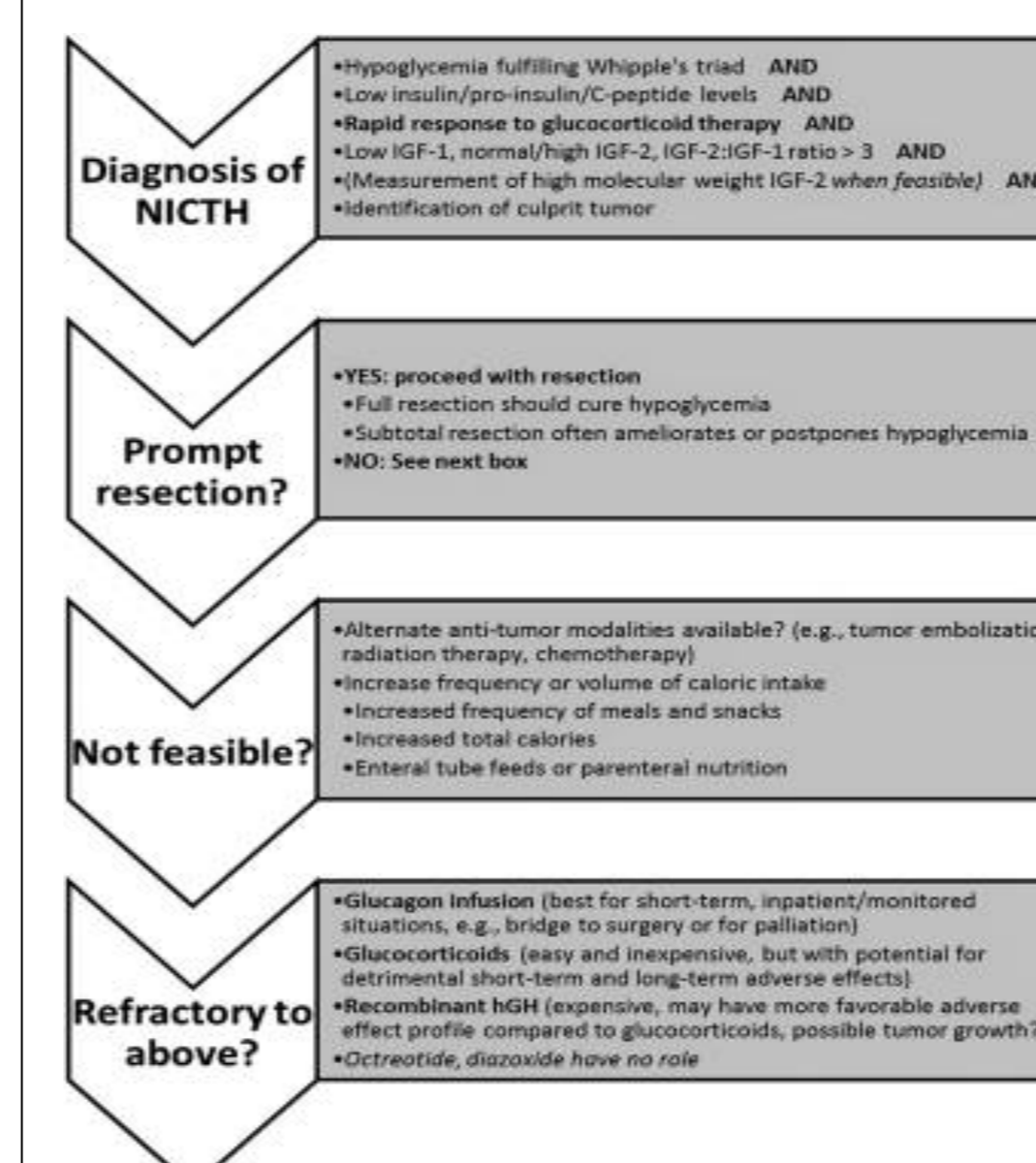


- IGF-II production by tumour
- Acts on insulin receptor to ↑ glucose utilisation in muscle + ↓ gluconeogenesis
- Suppresses insulin, glucagon and GH release
- Infiltration of hepatic tissue by tumour
- Destruction of adrenal glands by tumour / haemorrhage

Diagnosis

- Key feature is ↓↓glucose/insulin/C-peptide/-hydroxybutyrate PLUS ↑ free IGF-II, IGF-II:IGF-I ratio, pro IGF-II levels

Management



- Glucocorticoids
 - Suppresses production + increase clearance of IGF-II
 - Used in ~25% of cases
 - Typically 30 – 60mg /day needed
- Recombinant GH
 - Caution re: possible effect on tumour growth

References

1. Bodner TW et al. (2014) Management of non-islet cell tumor hypoglycemia: a clinical review. JCEM; 99(3): 713-22
2. Fukuda I et al. (2006) Clinical features of insulin-like growth factor-II producing non-islet-cell tumour hypoglycemia. Growth Horm IGF Res; 16(4): 211-6